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Quantification of Toxicological Effects Section of the Drinking Water Criteria Document on Lead (Draft)

Life Systems, Inc., Cleveland, OH

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16. ABSTRACT

The Criteria and Standards Division (CSD), U.S. Environmental Protection Agency has prepared a section on the toxicological effects of lead exposure through drinking water. This lead section may be read with the Air Quality Criteria Document for lead prepared by the Environmental Criteria and Assessment Office (ECAO), U.S. EPA. The toxicological effects section is a review of the following topics:

- Biochemical Indices of Lead Exposure
- Metabolism of lead
- Assessment of lead exposures and absorption in human populations
- Biological effects of lead exposure
- Evaluation of human health risks associated with exposure to lead

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QUANTIFICATION OF TOXICOLOGICAL EFFECTS OF LEAD

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FOREWARD AND ACKNOWLEDGMENT

The Quantification of Toxicological Effects section of a Criteria Document is normally based on health effects information contained in Sections I to VII of the Criteria Document. In this case, it was decided that an existing report on the health effects of lead, entitled "Air Quality Criteria for Lead," prepared by the Environmental Criteria and Assessment Office, U. S. Environmental Protection Agency (USEPA 1984), was suitable as a background document that could substitute for the normal contents of Sections I to VII. Much of the following text regarding the non-carcinogenic and carcinogenic effects of lead has been extracted, entirely or in part, from that document.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of non-carcinogenic effects, an Acceptable Daily Intake (ADI) is calculated. An Adjusted Acceptable Daily Intake (AADI) and Health Advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{(\text{NOAEL or LOAEL in mg/kg/day})(\text{Body Weight in kg})}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking Water Volume in L/day}} = \text{mg/L}$$

where:

NOAEL = no-observed-adverse-effect level.

LOAEL = lowest-observed-adverse-effect level.

Body weight = 70 kg for adult or 10 kg for child.

Drinking water volume = 2 L per day for adults or 1 L per day for children.

Uncertainty/Safety Factor = 10, 100 or 1,000.

Utilizing these equations, the following drinking water concentrations are developed for non-carcinogenic effects:

1. A one-day HA for 10-kg child.
2. A one-day HA for 70-kg adult.
3. A ten-day HA for 10-kg child.
4. A ten-day HA for 70-kg adult.
5. A lifetime AADI for a 70-kg adult.

The distinctions made between the HA calculations (items 1 through 4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1 to 2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon non-carcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivity to toxic chemicals.

An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS 1977, 1980) is typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.

- An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more species, but human data are not available.

- An uncertainty factor of 1,000 is used when limited or incomplete acute or chronic toxicity data are available or when only the acute or chronic toxicity data identifying a LOAEL (but not NOEL/NOAEL) for one or more species are available.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines for selection of an uncertainty factor, but that must be considered include: (1) the quality of the toxicology data, (2) the significance of the adverse effect and (3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (there is evidence that some lead salts are carcinogenic following oral exposure in animals), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical via drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for non-continuous animal feeding, non-lifetime studies and differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 liters of water per day. The multi-stage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models, such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very

nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as (1) incomplete knowledge concerning the health effects of contaminants in drinking water, (2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results and (3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually available only for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Calculation of the ADI and AADI values for lead requires several changes in the normal approach described above. This is because most studies in humans evaluate the degree of lead exposure by measuring the concentration of lead in the blood (PbB), rather than by measuring lead ingestion. This requires that the NOAEL first be described in terms of a PbB, and then the oral exposure which produces that PbB must be calculated. The principal disadvantage to this approach is the additional uncertainty involved in such a calculation. On the other hand, since exposure is based on PbB levels, it is possible to consider studies in humans in which neither the route nor

average daily exposure is known. For these reasons, in the following descriptions of studies on the toxicological effects of lead in humans, attention is focused on defining the PbB level which is not associated with adverse effects, regardless of route of exposure. From the PbB value selected as the NOAEL, an average oral daily intake level which would produce this PbB is calculated, and this is taken as the ADI.

A. Non-Carcinogenic Effects

Lead is a gray-white metal that, because of its easy isolation and low melting point, was among the first of the metals to be utilized by humans. Lead is relatively abundant in the earth's crust, most commonly in the form of galena (lead sulfide). Lead is the heaviest member in Group IV-B of the periodic table (atomic number = 82, atomic weight = 207). The inorganic chemistry of lead is dominated by the divalent (+2) oxidation state. Most common lead salts are either sparingly soluble (e.g., PbF_2, $PbCl_2$) or virtually insoluble (e.g., $PbSO_4$, $PbCrO_4$) in water, although a few salts are readily soluble (e.g., $Pb(NO_3)_2$, $Pb(CH_3COO)_2$). A large number of organo-lead compounds are known, and these nearly always involve the tetravalent (+4) oxidation state of lead. The chemistry of these compounds is complex, and is quite distinct from the chemistry of inorganic lead (USEPA 1977).

Gastrointestinal absorption of lead is highly variable,

depending on chemical form, dietary intake and age. For example, absorption from liquids is about five to eight times the absorption from food (USEPA 1977). Typical gastrointestinal absorption of lead in adults is about 5% to 10%, but is higher (24% to 53%) in infants and young children (USEPA 1977). Deposition and absorption of inhaled lead depends on particle size, chemical form and rate and depth of breathing. In one study in human volunteers (Muir and Davies 1967), 6% to 16% deposition was observed.

Absorbed lead distributes to all tissues of the body, but tends to accumulate in bone. In adults, over 94% of total lead body burden is in bone (Schroeder and Tipton 1968). The major route of excretion of absorbed lead in humans is the urine (76%), with smaller amounts in feces (16%) and hair, nails and sweat (4%) (Rabinowitz et al. 1973). In human subjects fed a constant level of ^{204}Pb, blood levels reached a steady state in about 100 days, and lead was cleared from the blood with a half-time of about 19 days after exposure ceased (Rabinowitz et al. 1973). The concentration of lead in soft tissues of humans usually reaches a steady state by age 20 (Barry 1975), while levels in bone tend to increase at least until age 50 to 60 (Barry and Mossman 1970).

1. Short-Term Exposure

Acute lead poisoning is not common, and is less thoroughly

studied that chronic lead poisoning. Estimates of acute oral lethal doses in animals depend on chemical form, but are usually quite high (500 to 30,000 mg/kg) (NIOSH 1983).

Studies in animals indicate that the perinatal period of ontogeny is a time of particular sensitivity to lead exposure. Table VIII-1 is a partial summary of a large number of studies in which effects have been detected in offspring of mothers exposed to lead during gestation and/or after delivery. Ingestion by nursing females of water containing levels as low as 0.004% (40 mg/L, corresponding to a dose of about 4 mg/kg/day) causes effects on neurotransmitter metabolism in the offspring, and higher exposure levels result in a number of morphologic, biochemical and electrophysical changes.

Perinatal exposure to lead also produces a number of behavioral alterations in young animals. For example, Grant et al. (1980) exposed rats indirectly to lead in utero and during lactation through the mother's milk and, after weaning, directly through drinking water containing the same lead concentrations their respective dams had been given. There were delays in the development of surface righting and air righting reflexes in subjects given water containing 0.005% or 0.025% lead (50 or 250 mg/L, corresponding to about 5 or 25 mg/kg/day). Other reflexive patterns showed no effect. The median blood lead concentration for the 0.005% subjects at postnatal day 11 was 35 ug/L.

Table VIII-1 Partial Summary of Studies in Rats of Lead Effects During Perinatal Development[a]

Exposure protocol	Estimated daily dose[b] (mg/kg/day)	Observed effects	Reference
0.004% $Pb(Ac)_2$ in dams' drinking water PND 0-35	4	Decline in synthesis and turnover of striatal DA	Govoni et al. (1979, 1980), Memo et al. (1980a, 1981)
0.02% $PbCl_2$ in dams' drinking water from gestation thru PND 0-21	20	1. Transient 30% reduction in cytochrome content of cerebral cortex 2. possible uncoupling of energy metabolism 3. delays in development of energy metabolism	McCauley and Bull (1978), McCauley et al. (1979), Bull et al. (1979), Bull (1983)
0.1% $Pb(Ac)_2$ in dams' drinking water PND 0-32	100	Significant inhibition in myelin deposition and maturation in whole brain	Stephens and Gerber (1981)
0.2% $PbCl_2$ in dams' drinking water from gestation thru PND 0	200	Less mature synaptic profile in cerebral cortex at PND 15	McCauley and Bull (1978), McCauley et al. (1979)
		30% reduction in synaptic density in cerebral cortex at PND 15 (returned to normal at PND 21)	McCauley et al. (1982)
0.2% $Pb(Ac)_2$ in dams' drinking water PND 0-25	200	15-30% reduction in synaptic profiles in hippocampus	Cambell et al. (1982)

continued-

[a] Abbreviations used are: PND = post-natal day; $Pb(Ac)_2$ = lead acetate; MES = maximal electroshock seizure; VER = visual evoked response; NE = norepinephrine; DA = dopamine; GABA = gamma amino-butyric acid; GMP = guanosine monophosphate; 5HT = serotonin.

[b] Assuming daily consumption of 0.1 L of water per kilogram body weight (Arrington 1972).

Table VIII-1 - continued

Exposure protocol	Estimated daily dose (mg/kg/day)	Observed effects	Reference
0.2% $Pb(Ac)_2$ in dams' drinking water PND 0-20	200	More rapid appearance and incrased severity of MES response	Fox et al. (1978, 1979)
0.2% $Pb(Ac)_2$ in dams' drinking water PND 0-21	200	1. Increased latencies and decreased amplitudes of primary and secondary components of VER 2. decreased conduction velocities in visual pathways 3. 25-50% decrease in scotopic visual acuity 4. persistent decreases in visual acuity and spatial resolution at PND 90	Fox et al. (1977), Impelman et al. (1982), Cooper et al. (1980), Winneke (1980), Fox and Wright (1982), Fox et al. (1982)
0.2% $Pb(Ac)_2$ in dams' drinking water PND 0-21	200	1. 23% decrease in NE levels of hypothalamus and striatum 2. increased turnover of NE in brainstem	Goldman et al. (1980)
0.25% $Pb(Ac)_2$ in dams' drinking water PND 0-35	250	Decline in synthesis and turnover of striatal DA	Govoni et al. (1978a)
0.25% $Pb(Ac)_2$ in dams' drinking water PND 0-35	250	Increase in DA synthesis in frontal cortex and nuc. accumbens (10-30% and 35-45%, respectively)	Govoni et al. (1979, 1980), Memo et al. (1980a, 1981)
0.25% $Pb(Ac)_2$ in dams' drinking water PND 0-35	250	1. 50% increase in DA binding to striatal D_2 receptors 2. 33% decrease in DA binding to nuc. accumbens D_2 receptors	Lucchi et al. (1981)

continued-

Table VIII-1 - continued

Exposure protocol	Estimated daily dose (mg/kg/day)	Observed effects	Reference
0.25% $Pb(Ac)_2$ in dams' drinking water PND 0-42	250	1. 31% increase in GABA specific binding in cerebellum; 53% increase in GMP activity 2. 36% decrease in GABA-specifc binding in striatum; 47% decrease in GMP activity	Govoni et al. (1978b, 1980)
0.25% $Pb(Ac)_2$ in dams' drinking water PND 0-21; 0.004% or 0.25% until PND 42	250	1. 12% and 34% elevation of GABA binding in cerebellum for 0.004% and 0.25%, respectively 2. 20% and 45% decreases in GABA binding in striatum for 0.004% and 0.25%, respectively	Memo et al. (1980b)
0.4% $PbCO_3$ in dams' drinking water PND 0-30	400	Retardation in temporal sequence of hippocampal dendritic development	Alfano and Petit (1982)
0.5% $Pb(Ac)_2$ in dams' drinking water PND 0-21	500	10-15% reduction in number of axons in optic nerve; skewing of fiber diameters to smaller sizes	Tennekoon et al. (1979)

Adapted from USEPA (1984).

The effect of lead on development of motor function was also investigated by Overman et al. (1981). Exposure of rat pups to lead was limited to the period from parturition to weaning and occurred through adulteration of the dams' drinking water with lead acetate (0.01% or 0.1%, equivalent to about 10 or 100 mg/kg/day). Overall, the ability to remain on a rotating rod was significantly impaired ($P < 0.01$) at 0.1%, and tended to be impaired ($0.10 > P > 0.05$) at 0.01%.

Generally similar results are obtained when suckling or young rats are exposed to lead directly (as opposed to indirect exposure via the mother). Tables VIII-2 and VIII-3 summarize some studies of this sort. Cory-Slechta and Thompson (1979) exposed Sprague-Dawley rats to 0.0025%, 0.015%, or 0.05% drinking water solutions of lead (as lead acetate) starting at post-natal day (PND) 20-22. Operant conditioning on a fixed-interval 30-second schedule of reinforcement (food pellet delivered upon the first bar-press occurring at least 30 sec. after preceding pellet delivery) began at PND 55-60. Blood lead concentrations measured at approximately PND 150 were reported in graphical form roughly as follows: 0.0025% solution group, 5-10 ug/dL PbB; 0.015% group, 25-30 ug/dL PbB; 0.05% group, 40-45 ug/dL PbB. Subjects exposed to 0.0025% or 0.015% lead solutions showed a "significantly" (no probability value reported) higher median response rate than matched controls during the first 30 sessions of training; response rates continued to be significantly higher over the next 60 sessions

Table VIII-2 Behavioral Effects of Direct Lead Exposure in Young Rats[a]

Reference	Lead Exposure: Pb conc. (medium)	Lead Exposure: Period (route)	Estimated daily dose[b] (mg/kg/day)	Testing paradigm (task)	Age at testing	Behavioral results
Overmann (1977)		PND 3-21 (gavage)	C = 0 Pb_1 = 5 Pb_2 = 15 Pb_3 = 45	Adversive conditioning	26-29 days	Pb_3-Ss sig. slower in acquisition and extinction of active avoidance response; no sig. diffs. for passive avoidance. All Pb groups failed to inhibit responses as well as C-Ss. No sig. diffs. on E-maze tasks, except $Pb_{2,3}$-Ss sig. worse than C-Ss when on tactile discrim.
Dietz et al (1978)		PND 3-30 (gavage)	C = 0 Pb = 200	Operant (minimum 20-sec pd. between bar-presses)	90 days	Short IRTs (<4 sec) more prevalent in Pb-Ss than in C-Ss, but did not result in different reward rates; Pb-Ss showed higher variability in response-rate under d-amphetamine treatment.

continued-

[a]Abbreviations:
C = control group
FI = Fixed interval
IRT = Inter resposne time
PND = Post-natal day
Ss = Subjects
? = Information not given

[b]Assuming consumption of 100 mL water/kg body weight (Arrington 1972).

Table VIII-2 - continued

Reference	Lead Exposure: Pb conc. (medium)	Lead Exposure: Period (route)	Estimated daily dose[a] (mg/kg/day)	Testing paradigm (task)	Age at testing	Behavioral results
Cory-Slechta and Thompson (1979)	C = 0 Pb_1 = 0.0025% Pb_2 = 0.015% Pb_3 = 0.05% (water)	a. PND 20-70 or b. PND 20-150	C = 0 Pb_1 = 2.5 Pb_2 = 15 Pb_3 = 50	Operant (FI-30 sec)	55-140 days	Increased response rate and inter-S variability in groups $Pb_{1a,b}$ and Pb_2; decreased response rate in group Pb_3; effects in Pb_{1a} reversed after exposure terminated.
Cory-Slechta et al. (1981)	C = 0 Pb_1 = 0.005% Pb_2 = 0.015% (water)	PND 21-?	C = 0 Pb_1 = 5 Pb_2 = 15	Operant (minimum duration bar-press)	55-? days	Pb groups impaired: decreased response durations; increased response latencies; failure to improve performance by external stimulus control.
Milar et al. (1981b)		PND 4-31 (gavage)	C = 0 Pb_1 = 25 Pb_2 = 100 Pb_3 = 200	Operant (spatial alternation levers)	50 days	No sig. differences between C-Ss and Pb-Ss.

[a]Assuming consumption of 100 mL water/kg body weight (Arrington 1972).

Adapted from USEPA (1984).

Table VIII-3 Neurological Effects of Direct Lead Exposure in Young Rats[a]

Exposure protocol	Estimated daily dose (mg/kg/day)	Observed effects	Reference
0.1% Pb^{++} in chow PND 0-90	50	Decreased density of oligodendrocytes in cerebral cortex	Reyners et al. (1979)
Gastric intubation PND 2-14	75	1. 20% decline in striatal DA levels at PND 35 2. 35% decline in striatal DA turnover by PND 35 3. Transient depression of DA uptake at PND 15 4. Possible decreased DA terminal density	Jason and Kellogg (1981)
0.25-1% $Pb(Ac)_2$ in drinking water[b] PND 0-60	250-1,000	1. 40-50% reduction of whole-brain ACh by PND 21 2. 36% reduction by PND 30 (return to normal values by PND 60)	Modak et al. (1978)
0.5-1% $Pb(Ac)_2$ in drinking water[b] PND 0-60	500-1,000	1. Increased sensitivity to seizures induced by GABA blockers 2. Increase in GABA synthesis in cortex and striatum 3. Inhibition of GABA uptake and release by synaptosomes from cerebellum and basal ganglia 4. 70% increase in GABA-specific binding in cerebellum	Silbergeld et al. (1979, 1980a)
1% $PbCO_3$ in chow PND 0-60	500	Retardation of cortical synaptogenesis over and above any nutritional effects.	Averill and Needleman (1980)

[a]Abbreviations:
PND = Post-natal day
GABA = gamma aminobuyric acid
ACH = Acetyl choline
DA = Dopamine

[b]Assuming consumption of 100 mL water/kg/day and 50 g chow/kg/day (Arrington 1972).

Adapted from USEPA (1984).

for the 0.0025% group and over the next 30 sessions for the 0.015% group (at which points training terminated for each group). Moreover, latencies to the first response in the 30-sec. interval (the beginning of the typical "fixed-interval scallop" cumulative response pattern) were significantly shorter in the 0.0025% and 0.015% groups. However, response rates for the group exposed to the 0.05% solution were significantly lower than the control group's rates for the first 40 sessions; correspondingly, response latencies were longer for the highest exposure group.

Other work by Cory-Slechta et al. (1981) repeated the earlier study's exposure regimen (using 0.005% and 0.015% solutions) and examined the effects on another aspect of operant performance. In this study the subjects were required to depress a bar for a specified minimum duration (0.5-3.0 sec.) before a food pellet could be delivered. Intersubject variability increased greatly in the lead-exposed groups. In general, though, treated subjects tended to shorten their response durations ($P = 0.04$ for the 0.005% group; $P = 0.03$ for the 0.015% group). This tendency would contribute toward a reduced rate of reinforcement, which is associated with (and perhaps accounts for) an observed tendency toward increased response latencies in the lead-exposed subjects ($P = 0.04$ in the 0.015% group).

Another form of developmental lag in gross activity around

post-natal days 15-18, as measured in an automated activity chamber, was reported by Jason and Kellogg (1981). Rats were intubated on days 2 to 14 with lead at 25 mg/kg (PbB = 50.07 $\pm$ 5.33 ug/dL) or 75 mg/kg (PbB = 98.64 $\pm$ 9.89 ug/dL). In this case, the effect was a delay in the characteristic decrease in activity that normally occurs in pups at that age (Campbell et al. 1969, Melberg et al. 1976); thus, lead-exposed pups were significantly more active that control subjects at post-natal day 18.

These alterations in behavior are indicative of altered neural functioning in the CNS, but whether such alterations represent significant impairment in overall functioning of the lead-exposed subjects is not clear. As some studies indicate, lead-treated subjects may actually perform better than non-treated control subjects on certain learned tasks (Winneki et al. 1982b, Driscoll and Stegner 1976, Gross-Selbeck and Gross-Selbeck 1981). Taken as a whole, these studies suggest that lead exposure results in a tendency to respond more rapidly or "excessively", regardless of whether or not such responding is appropriate for the reinforcement contingencies of an experiment. However, this idea remains to be firmly established.

Acute lead intoxication resulting from a single high dose of lead is rare in humans. Symptoms of acute lead poisoning include vomiting, abdominal pain, hemolysis, liver damage and

reversible tubular necrosis. Ingestion of a large but undetermined amount of red lead (lead tetroxide) by a 21-year-old male resulted in severe hemolysis and blood lead levels of 130 ug/dL before treatment was begun three days after ingestion (Nortier et al. 1980). Free hemoglobin levels in the serum were normal six days after exposure, and liver function tests were normal after four weeks.

A similar response to lead was observed after four drug addicts injected themselves intravenously with opium and lead acetate suspended in water (Beattie et al. 1979). Blood lead levels of 180 ug/dL were observed upon admission of one subject to the hospital ten days after injection of about 900 mg lead acetate. Symptoms included severe abdominal pain, headache and generalized limb pains. The time interval between injection of the drugs and onset of symptoms varied from two days in the two most severe cases to two months in the patients with mild illnesses. Liver lead values ranged from 111 to 824 mmol/kg liver wet weight (23 to 170 g/kg), as compared with values of 4.2 to 24.6 mmol/kg (0.87 to 5.1 g/kg) found in cases of industrial lead poisoning.

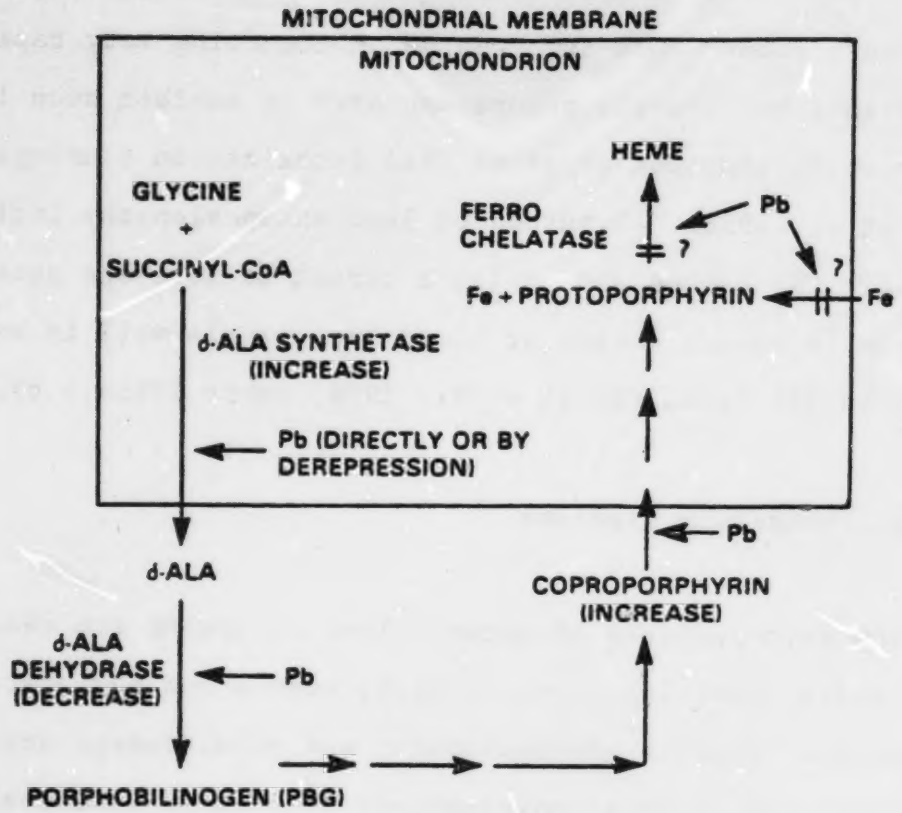
Subacute exposure may produce a syndrome of neurologic disorders. Early signs of neuropathy (which may develop within weeks of initial exposure) include dullness, restlessness, irritability, poor attention span, headaches, muscular tremor, hallucinations and loss of memory. These symptoms may pro-

gress to delirium, mania, convulsions, paralysis, coma and death. The onset of such symptoms can often be quite abrupt, with convulsions, coma and even death occurring very rapidly in patients who shortly before appeared to exhibit much less severe or no symptoms of acute lead intoxication (Cumings 1959, Smith et al. 1938). Symptoms of lead encephalopathy indicative of severe CNS damage and posing a threat to life are generally not seen in adults except at blood lead levels well in excess of 100 to 120 ug/dL (Smith et al. 1938, Kehoe 1961a,b,c).

2. Long-Term Exposure

The main symptoms of chronic lead poisoning are abdominal pain, colic, vomiting, constipation, anemia and peripheral neuropathy. Whereas encephalopathy and renal damage are considered the most serious complications of chronic lead toxicity in man (Nortier et al. 1980), the hematopoietic system may be more sensitive. Anemia resulting from decreased erythrocyte production and increased cell destruction is often the earliest manifestation of chronic lead poisoning.

a. Effects of Lead on Hematopoiesis. Lead inhibits several enzymes involved in heme biosynthesis (Figure VIII-1). In adult humans, levels of 15 to 20 ug/dL and 25 to 30 ug/dL result in 40% and 70% inhibition of delta-aminolevulinic acid dehydratase (ALAD) activity, respectively. In children, 40% inhibition occurs at PbB values of 5 to 20 ug/dL, and 70%



Adapted from USEPA (1984).

Figure VIII-1 Sites of Lead Inhibition of Heme Biosynthesis

inhibition is observed at 20 to 25 ug/dL (Zielhuis 1975). Granick et al. (1973) observed ALAD inhibition at PbB values of 15 ug/dL and higher, and similar results were reported by Hernberg and Nikkanen (1970). Measuring a decrease in erythrocyte ALAD activity correlates better with PbB values and is more sensitive than monitoring a decrease in hemoglobin (Selander and Cramer 1970, Tola et al. 1973). Inhibition of ALAD results in increased urinary concentrations of delta-aminolevulinic acid (ALA). A significant increase in urinary ALA occurs at PbB values of 40 to 50 ug/dL (Tola 1973, Selander and Cramer 1970, Haeger-Aronsen et al. 1974).

Lead also interferes with the final step in heme biosynthesis, the chelation of iron by protoporphyrin IX. The work of Zielhuis (1975) shows that elevation of free erythrocyte porphyrin is a more sensitive indicator of lead exposure than is inhibition of ALAD. However, increased free erythrocyte porphyrin is not a specific indicator of lead-induced anemia (Roels et al. 1978).

A few studies have reported effects of lead on hemoproteins other than hemoglobin. For example, the rate of cytochrome P-450-mediated drug metabolism was depressed in two cases of lead poisoning (PbB = 60 and 72 ug/dL), but not in ten cases where lead levels ranged from 20 to 60 ug/dL (Alvares et al. 1975). Although other hemoproteins may be affected by lead, the evidence suggests that they are not sensitive to

relatively low levels of exposure.

b. Effects of Lead on Blood Pressure. Hypertension is an important element in the etiology of cerebrovascular deaths. Dingwall-Fordyce and Lane (1963) reported a marked increase in the cerebrovascular mortality rate among heavily exposed lead workers as compared with the expected rate. These workers were exposed to lead during the first quarter of this century, when working conditions were poor.

Cramer and Dahlberg (1966) studied the incidence of hypertension in a population of 364 industrially exposed men in Sweden, 265 of whom had had long-term exposure to lead (ten or more years). They subdivided the workers into lead-affected and non-lead-affected groups, based on results from urinary coproporphyrin tests. There was no statistically significant difference in blood pressure between the groups, nor was the incidence of hypertension higher than that expected for non-exposed men in a similar population in Norway. Similar results (no evidence of increased hypertension among lead workers) have been described by Lane (1949) and Dreessen et al. (1941).

Beevers et al. (1980) reported results from an epidemiological study of hypertensive and normotensive persons in an area of Scotland where drinking water hardness is low and water lead levels are high. They found a significant association for males between high PbB values and high blood pressure

($P < 0.05$). The mean PbB values for hypertensive and normotensive men were 1.31 and 1.14 umol/L (27.1 and 23.7 ug/dL), respectively; for hypertensive and normotensive women, they were 1.09 and 0.94 umol/L (219 and 194 ug/dL). In a similar study in England, ingestion of soft water with high lead levels did not result in elevated PbB values, and no relationship was found with high blood pressure.

In a review of five fatal cases of lead poisoning in young children, degenerative changes in heart muscle were reported to be the proximate cause of death (Kline 1960). It is not clear, however, that such morphological changes are a specific response to lead intoxication. The overall evidence does not suggest that the heart is a critical target for lead effects.

c. Effects of Lead on the Renal System. Severe effects of lead on the renal system are seen both in persons dying of acute lead poisoning and in persons suffering from lead-induced anemia and/or encephalopathy. Effects are usually restricted to non-specific degenerative changes in renal tubular epithelial cells, with some degree of cellular necrosis. Cells of the proximal convoluted tubules are most severely affected.

Dysfunction of the proximal convoluted tubules (Fanconi's syndrome) is manifested by aminoaciduria, glycosuria and hyperphosphaturia. Chisolm (1962, 1966) found that nine of 23

children with lead encephalopathy had aminoaciduria, glycosuria and hypophosphatemia. Aminoaciduria was related to the severity of clinical toxicity and was most marked in children with encephalopathy. The aminoaciduria disappeared after treatment with chelating agents (Chisolm 1962).

Clarkson and Kench (1956) investigated renal function in men who were occupationally exposed to lead fumes (lead oxide and/or lead chromate). They found no clinical evidence of renal disease; however, they did observe a modest but significant increase in aminoaciduria. The duration of exposure to lead and the PbB values were not given, but up to 500 ug/L of lead was excreted in the urine. In a series of 15 infants hospitalized for lead poisoning, three had aminoaciduria with PbB values of 246, 399 and 1,798 ug/dL (Chisolm 1968).

Cramer et al. (1974) reported on a group of seven workers who had been exposed from less than one year to up to 30 years. Air lead concentrations in the workplace were not measured over the entire period, but were believed to exceed 0.2 mg/m^3. The average PbB was 100 ug/dL, ranging from 71 to 138 ug/dL, and all subjects had strikingly high urinary ALA excretion. Although aminoaciduria was not found and inulin clearance and renal blood flow were reported normal, some individuals with very long exposures were reported to have interstitial and peritubular fibrosis.

Cramer et al. (1974) suggested that there are at least two stages in the response of the human kidney to chronic lead exposure: (1) formation of nuclear inclusion bodies (probably reversible) with no impairment of renal function after short exposure; and (2) formation of interstitial fibrosis in the proximal tubular cells after four or more years of exposure. This latter stage is not characterized by any gross impairment of renal function, but it is doubtful whether the morphological changes are completely reversible. Whether or not a third stage exists (i.e., renal failure) remains questionable (Cramer et al. 1974).

Reduced glomerular filtration with an attendant rise in serum urea concentration is generally considered to be symptomatic of chronic lead nephropathy. It is accompanied by interstitial fibrosis, obliteration of glomeruli and vascular lesions (Morgan et al. 1966) and occurs at low levels of lead exposure relative to the levels associated with aminoaciduria. For example, in Cramer's study of seven lead workers, none had aminoaciduria, while three had low renal clearance of inulin (Cramer et al. 1974). In another study of men with occupational lead exposure (air lead levels not stated), four of eight individuals with PbB values of 48 to 98 ug/dL had reduced glomerular filtration rates (Wedeen et al. 1975). Biopsies on three of the subjects showed proximal tubule abnormalities. One subject with a PbB of 48 ug/dL showed asymptomatic renal failure (elevated blood urea nitrogen and serum creatinine

values). The PbB values of subjects with preclinical renal dysfunction (reduced glomerular filtration rate, but no elevation in blood urea or serum creatinine) ranged from 51 to 98 ug/dL. The average period of lead exposure was 4.25 years. On the basis of these studies, Wedeen et al. (1975) suggested that nephropathy may be an important occupational hazard in the U.S. lead industry.

In a series of 102 cases of lead poisoning studied by Lilis et al. (1968), undercompensated or decompensated renal failure was found in 17 patients, most of whom had been exposed to lead for more than 10 years. The mean PbB of the entire series was approximately 80 ug/dL, with a range from 42 to 141 ug/dL. The majority of this group had a history of several attacks of colic. Arterial hypertension followed chronic renal failure in 13 cases, with the renal impairment generally preceding the rise in blood pressure by several years.

Tabershaw and Cooper (1974) considered 7,032 workers who had been exposed to lead as a result of employment in either the battery or the lead-smelting industry between 1947 and 1970. Many were found to have PbB values in excess of 80 ug/dL. From a study of death records during the study period, the authors reported there was excess mortality due to "chronic nephritis and other renal scleroses" and "other hypertensive disease" (uremia, nephrosclerosis and other renal disease).

Renal effects have also been observed in persons exposed to lead in domestic water supplies. In 970 households studied in Scotland, Campbell et al. (1977) found an association between elevated PbB values and renal insufficiency, as indicated by elevated serum urea concentration. Of the 970 households from which water samples were obtained, 249 had lead levels greater than 100 ug/L. Many samples exceeded this limit by a large margin, with the highest value being 8,500 ug/L. Among 54 age- and sex-matched pairs of subjects, those with elevated serum urea levels had PbB values in the range of 10.4 to 103 ug/dL. This compared to PbB values ranging from 10.4 to 62 ug/dL for those without elevated serum urea levels.

From these and other studies, it appears that the kidney is sensitive to lead-induced glomerular-vascular damage, with a threshold perhaps below a PbB value of 50 ug/dL. These renal conditions are considered to be precursors of hypertension.

d. Reproductive and Teratogenic Effects of Lead. It has been known since before the turn of the century that lead may exert adverse effects on human reproduction. Legge (1901) reported an increased frequency of miscarriages and stillbirths in women working in the lead trades during the latter half of the 19th century. Lane (1949) reported on the outcome of 15 pregnancies among 150 women working under conditions of moderate lead exposure (via air). Three of these women had miscarriages (an incidence seven times normal), although the numbers

were too small to be statistically significant. A Japanese study among women with PbB values of 110 to 317 ug/dL indicated a greater incidence of miscarriages and reduced fertility, but there was no significant correlation with the PbB values Nogaki 1958).

The incidence of premature fetal membrane rupture in term and preterm infants was higher in an area 30 to 50 miles west of a lead mining area of Missouri than in a Missouri urban area remote from lead mining activities (1% versus 0.41%) (Fahim et al. 1976). Maternal and fetal PbB values at birth differed significantly for normal births versus births with premature membrane rupture. Mean maternal and fetal PbB values for the normal deliveries were about 14 and 4 ug/dL, respectively, whereas the mean PbB values were about 26 and 13 ug/dL, respectively, for mothers and infants with membrane rupture.

Wibberley et al. (1977) examined a series of 126 births in Birmingham, England, and found that placental lead levels in the case of stillbirth or neonatal death were significantly higher than in the case of normal births. Placental levels were greater than 1.5 ug/g in only 7% of the normal births, whereas placental levels were greater than this in 61% of the stillbirths or neonatal deaths.

There is some evidence that lead affects fertility as well as the viability of the fetus. Lancranjan et al. (1975)

reported that significant levels of teratospermia occurred among men working in a lead storage battery factory. Their PbB values were 41.0 to 74.5 ug/dL. The extent to which abnormally shaped spermatozoa affect fertilization, however, has not been established.

e. Effects of Lead on the Nervous System. It has been recognized for many years that chronic exposure to lead may result in severe neurological disorders. Overt neuropathy is usually associated with PbB values in excess of 60 ug/dL (Lilis et al. 1977, Irwig et al. 1978, Dahlgren et al. 1978, Baker et al. 1979, Haenninen et al. 1979, Spivey et al. 1979, Fischbein et al. 1980, Hammond et al. 1980). A number of workers have sought to assess the neurotoxic effects of lead using criteria more sensitive than overt neuropathy and there is a considerable body of data of this sort derived from animal studies. However, this material will not be discussed here, because there is also a large body of data from human studies that can be used, thereby avoiding the uncertainty associated with extrapolating from animals to humans.

(1) Lead-Induced Neuropathy in Adults. Morgan and Repko (1974) reported deficits in hand-eye coordination and reaction time in an extensive study of behavioral functions in 190 lead-exposed workers (mean blood lead level = 60.5 ug/dL). The majority of the subjects were exposed for 5 to 20 years. Similar studies (Arnvig et al. 1980, Grandjean et al. 1978,

Haenninen et al. 1978, Mantere et al. 1982, Valciukas et al. 1978) have found disturbances in visual motor performance, IQ test performance, hand dexterity, mood, nervousness and coping in lead workers with blood lead levels of 50 to 80 ug/dL. On the other hand, Milburn et al. (1976) found no differences between control and lead-exposed workers as judged by numerous psychometric and other performance tests.

Seppalainen et al. (1975) observed slowed nerve conduction velocity (NCV) in lead workers whose PbB levels were as low as 50 ug/dL and had never exceeded 70 ug/dL during the entire exposure period (mean = 4.6 years). Similarly, Melgaard et al. (1976) observed a clear association between lead exposure and peripheral nerve dysfunction in automobile mechanics exposed to tetra-ethyl lead and other lead compounds in lubricating and high-pressure oils. Half of the workers (10 of 20) had elevated PbB levels (60 to 120 ug/dL) and showed definite electromyographic deficits. The mean blood lead level for the control group was 18.6 ug/dL.

More recent studies by Araki et al. (1980), Ashby (1980), Bordo et al. (1982), Johnson et al. (1980), Seppalainen et al. (1979) and Seppalainen and Hernberg (1980, 1982) have confirmed a dose-dependent slowing of NCV in lead workers with PbB levels below 70 to 80 ug/dL. Sappalainen et al. (1979) observed NCV slowing in workers with blood lead levels ranging from 29 to 70 ug/dL, and Seppalainen and Hernberg (1980, 1982) found NCV

slowing in workers with maximum PbB levels of 30 to 48 ug/dL, but not among workers with levels below 30 ug/dL. Buchthal and Behse (1979), Lilis et al. (1977) and Paulev et al. (1979), in contrast, found no signs of neuropathy at PbB levels below 80 ug/dL. Thus, considerable evidence exists that peripheral nerve dysfunction occurs in adults at PbB levels as low as 30 to 50 ug/dL. The question as to whether these reflect mild, reversible effects (Buchthal and Behse 1981) or are true early warning signals of progressively more serious peripheral neuropathies (Feldman et al. 1977, Sappalainen and Hernberg 1980) is still a matter of some dispute. Nevertheless, it is clear that these effects represent a departure from normal neurologic functioning, and their potential relationship to more serious effects establishes a basis for prudence in interpreting their potential health significance.

(2) Lead-Induced Neuropathy in Children. Overt symptoms of encephalopathy similar to those that occur in adults have been reported to occur in infants and young children (Prendergast 1910, Blackfan 1917, McKhann and Vogt 1926, Giannattasio et al. 1952, Cumings 1959, Tepper 1963, Chisolm 1968). A markedly higher incidence of severe encephalopathic symptoms and death among lead-exposed children than adults may reflect the greater difficulty of recognizing early symptoms in young children (Lin-Fu 1973). Available data indicate that PbB levels associated with acute encephalopathy symptoms are lower among children than adults. The most extensive

compilation of information on a pediatric population is a summarization by NAS (1972) of data from Chisolm (1962, 1965) and Chisolm and Harrison (1956). This data compilation relates occurrence of acute encephalopathy and death in children in Baltimore to PbB levels determined by the Baltimore City Health Department. Signs of encephalopathy (hyperirritability, ataxia, convulsions, stupor and coma) were associated with PbB levels of approximately 90 to 800 ug/dL (mean = 330 ug/dL). The distribution of PbB levels associated with death (mean = 327 ug/dL) was essentially the same as for levels associated with encephalopathy. These data suggest that PbB levels capable of producing death in children are essentially identical to those associated with acute encephalopathy, and that such effects are usually manifested in children starting at PbB levels of approximately 100 ug/dL. Other evidence from scattered medical reports (Gant 1938, Smith et al. 1938, Bradley et al. 1956, Bradley and Baumgartner 1958, Cumings 1959, Rummo et al. 1979) suggests that acute encephalopathy in the most highly susceptible children may be associated with blood lead levels in the range of 80 to 100 ug/dL.

Lasting neurotoxic sequelae of overt lead intoxication in children in the absence of acute encephalopathy have also been reported. Byers and Lord (1943), for example, reported that 19 out of 20 children with previous lead poisoning later made unsatisfactory progress in school, presumably due to sensorimotor deficits, short attention span and behavioral disorders. These

effects have since been confirmed in children with known high exposures tc lead, but without a history of life-threatening forms of acute encephalopathy (Chisolm and and Harrison 1956, Cohen and Ahrens 1959, Kline 1960).

Perlstein and Attala (1966) reported neurological sequelae in 140 of 386 children (37%) following lead poisoning without encephalopathy. Sequelae included mental retardation, seizures, cerebral palsy, optic atrophy and visual-perceptual problems with minimal intellectual impairment. The severity of sequelae was related to the severity of the earlier observed symptoms.

De la Burde and Choate (1972, 1975) observed neurological dysfunctions, fine motor dysfunction, impaired concept formation and altered profiles in 70 preschool children exhibiting pica. These children displayed elevated PbB levels (above 30 ug/dL in all cases; mean = 59 ug/dL) in comparison with 70 matched control subjects not engaging in pica. Subjects were drawn from the Collaborative Study of Cerebral Palsy, Mental Retardation and Other Neurologic Disorders of Infancy and Childhood (Broman et al. 1975). In a follow-up study on the same children (at seven to eight years of age), De la Burde and Choate (1975) reported continuing CNS impairment in the lead-exposed group, as assessed by a variety of physiological and neurological tests. In addition, seven times as many lead-exposed children were repeating grades in school or being referred to the school psychologist, despite the observation

that many of their PbB levels had by then decreased significantly from the initial study.

Odenbro et al. (1983) studied the psychological development of children (aged three to six years) seen in Chicago Department of Health clinics (August, 1976 to February, 1977). These workers evaluated scores from the Denver Development Screening Test (DDST) and Wechsler IQ scale (WPPSI) in relation to PbB levels obtained by repeated sampling during the three previous years. A significant correlation ($r = 0.435$, $P < 0.001$) was reported between decreased perceptual-visual-motor ability and mean PbB levels. Statistically significant ($P < 0.005$) deficits in verbal productivity and perceptual-visual-motor performance (measured by the WPPSI) were found for children with mean PbB levels of 30 to 40 ug/dL, versus control children with mean PbB levels below 25 ug/dL. These results are highly suggestive that neuropsychologic deficits are associated with PbB levels of 30 to 60 ug/dL in preschool children.

A population study was reported by Needleman et al. (1979), who used shed deciduous teeth as an index of lead exposure. Teeth were donated from 70% of a total population of 3,329 first and second grade children from two towns near Boston. Almost all children who donated teeth (2,146) were rated by their teachers on an eleven-item classroom behavior scale devised by the authors to assess attention disorders. A pre-

liminary analysis indicated a dose-response relationship between dentine lead content and behavior test results. A more detailed analysis was performed on 100 children with low dentine lead (<10 ppm) and 58 children with high dentine lead (>20 ppm). After consideration of a number of significant covariates (e.g., parental IQ and education), a significant difference ($P < 0.05$) between the low-lead and high-lead groups was found for two different IQ tests, 9 of the 11 behavioral tests and several measures of perceptual-motor behavior. In a subsequent report, Needleman (1982) demonstrated that the entire distribution of IQ scores was shifted downward in the high-lead group, with none of the children having a verbal IQ over 125.

Yule et al. (1981) studied the effects of lead exposure in a population of 195 children (aged 6 to 12 years). The PbB concentrations ranged from 7 to 32 ug/dL, and the children were assigned to one of four quartiles having the following PbB values: 7 to 10 ug/dL; 11 to 12 ug/dL; 13 to 16 ug/dL and 17 to 32 ug/dL. The tests of achievement and intelligence were similar to those used by Needleman et al. (1979). There were significant associations between PbB levels and scores on tests of reading, spelling and intelligence, but not of mathematics (Yule et al. 1981). In a subsequent report, Yule et al. (1983) dealt with the results pertinent to the attention deficits. While there were few differences between groups on the Rutter Scale, the summed scores on the Needleman question-

naire across PbB groupings approached significance (P = 0.096). Three of the questionnaire items showed a significant dose-response function ("Day Dreamer," "Does not Follow Sequence of Direction" and "Low Overall Functioning"). Nine of the eleven items were highly correlated with the children's IQ. Therefore, the Needleman questionnaire may be identifying IQ-related attention deficits, as opposed to measures of conduct disorders and socially maladaptive behavior (Yule et al. 1983). The authors noted that caution is necessary in interpreting their findings, in view of the crudity of the available measures of social factors and differences between countries in diagnosing attention deficit disorders.

Yule and Lansdown (1983) reported the results from a second and better designed study using similar methods and procedures with 194 children. These subjects lived near a busy roadway in a predominantly lower middle-class area of London. In contrast to the first pilot study, no statistically significant relationships were observed between PbB values and test achievement. Still, the authors stated there was some evidence between PbB levels and intelligence in working-class groups, but whether these are of a casual nature in either direction is unclear.

In a study by Winneke et al. (1982a), incisor teeth were donated by 458 children, aged seven to ten years, in Duisburg, Germany. Two extreme exposure groups were formed: a low-lead

group, with 2.4 ug/g mean tooth lead level (n = 26), and a high-lead group, with 7 ug/g mean tooth lead level (n = 16). The authors found a marginally significant decrease ($P < 0.10$) of five to seven IQ points and a significant decrease in perceptual-motor integration ($P < 0.05$).

Winneke et al. (1982b) carried out a study which involved 115 children living in the lead smelter town of Stolberg. Tooth lead (mean value = 6.16 ppm, range = 2.0 to 38.5 ppm) and PbB levels (mean = 13.4 ug/dL) were significantly correlated ($r = 0.47$; $P < 0.001$) for the children studied. Using stepwise multiple regression analysis, the authors found significant ($P < 0.05$) or marginally significant ($P < 0.10$) associations between tooth lead levels and measures of perceptual-motor integration, reaction time performance and four behavioral rating dimensions, including distractability.

Burchfiel et al. (1980), using computer-assisted spectral analysis of a standard EEG examination of 41 children from the study of Needleman et al. (1979), reported significant EEG spectrum differences in percentages of low-frequency delta activity and in spontaneous alpha activity of the high-lead children. Percentages of alpha- and delta-frequency EEG activity and results for several psychometric and behavioral testing variables (e.g., WISC-R full-scale IQ and verbal IQ, reaction time under varying delay) for the same children were then employed as input (or "features") in direct and stepwise

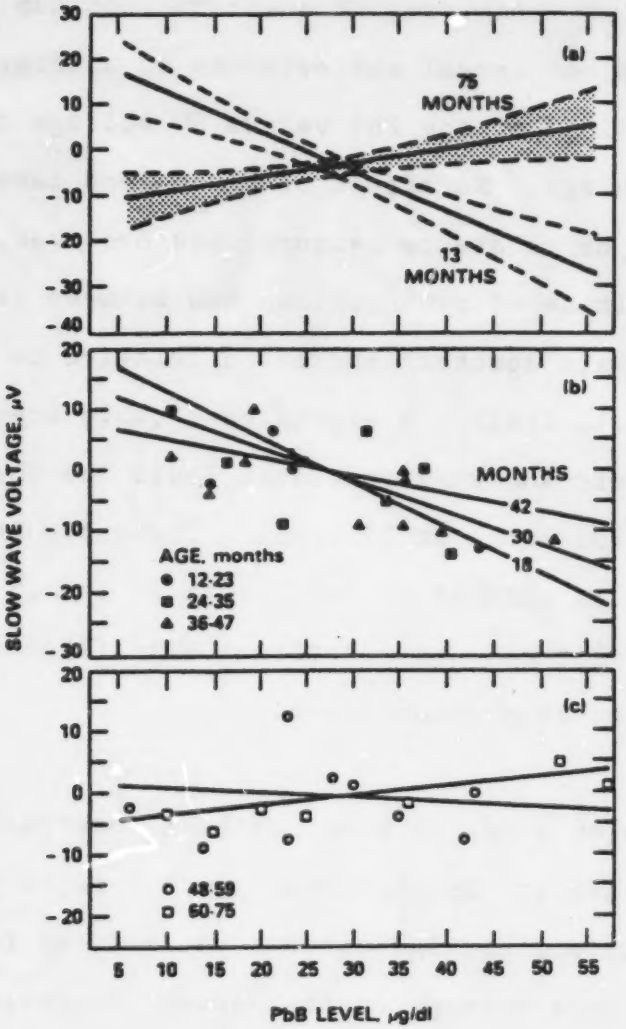
discriminant analyses. The separation determined by these analyses for combined psychological and EEG variables ($P < 0.005$) was reported to be strikingly better than the separation of low-lead from high-lead children obtained using either psychological ($P < 0.041$) or EEG ($P < 0.79$) variables alone. Unfortunately, no dentine lead or PbB values were reported.

The relationship between low-lead exposure and neurological function (including electrophysiological response) in children aged 13 to 75 months was extensively explored in a study conducted at the University of North Carolina in collaboration with the U. S. Environmental Protection Agency (Milar et al. 1980, 1981). Psychometric evaluation revealed lower IQ scores for children with PbB levels of 30 ug/dL or higher compared with children with PbB levels under 30 ug/dL. The observed IQ deficits were confounded by poor home caregiver environment scores in children with elevated PbB levels (Milar et al. 1980). No relationship between blood lead and hyperactive behavior (as indexed by standardized playroom measures and parent-teacher rating scales) was observed in these children (Milar et al. 1981).

Electrophysiological assessments, including analyses of slow potentials during sensory conditioning (Otto et al. 1981) and EEG spectra (Benignus et al. 1981), did provide evidence of CNS effects of lead in the same children. In contrast to psychometric and behavioral findings, a significant linear

relationship between PbB (ranging from 6 to 59 ug/dL) and slow wave (SW) voltage was observed (Otto et al. 1981), as depicted in Figure VIII-2. Analyses of quadratic and cubic trends in SW voltage did not reveal any evidence of a threshold for this effect. The slope of the PbB versus SW voltage function decreased with age. No effect of blood lead levels on EEG power spectra or coherence measures was observed, but the relative amplitude of synchronized EEG between left and right hemispheres (gain spectra) increased relative to PbB levels (Benignus et al. 1981). A significant cubic trend for gain between the left and right parietal lobes was found, with a major inflection point at 15 ug/dL. These findings suggest that EEG gain is altered at PbB levels as low as 15 ug/dL, although the clinical and functional significance of this measure has not been established.

A follow-up study of slow cortical potentials and EEG spectra in a subset (28 children, aged 35 to 93 months) of the original group was carried out two years later (Otto et al. 1982). Slow wave voltage during sensory conditioning again was a linear function of blood lead, even though the mean PbB level had declined by 11.4 ug/dL (from 32.5 ug/dL to 21.1 ug/dL). The similarity of SW results obtained at initial and follow-up assessments suggests that the observed alterations in this parameter of CNS function are persistent, despite a significant decrease in the mean PbB level during the two-year interval. No significant relationship between child IQ and



(a) Predicted SW voltage and 95% confidence bounds in 13- and 75-month-old children as a function of blood lead level.
(b) Scatter plots of SW data from children aged 13-47 months with predicted regression lines for ages 18, 30 and 42 months.
(c) Scatter plots for children aged 48-75 months with predicted regression lines for ages 54 and 66 months. These graphs depict the linear interaction of blood lead and age.

Adapted from USEPA (1984).

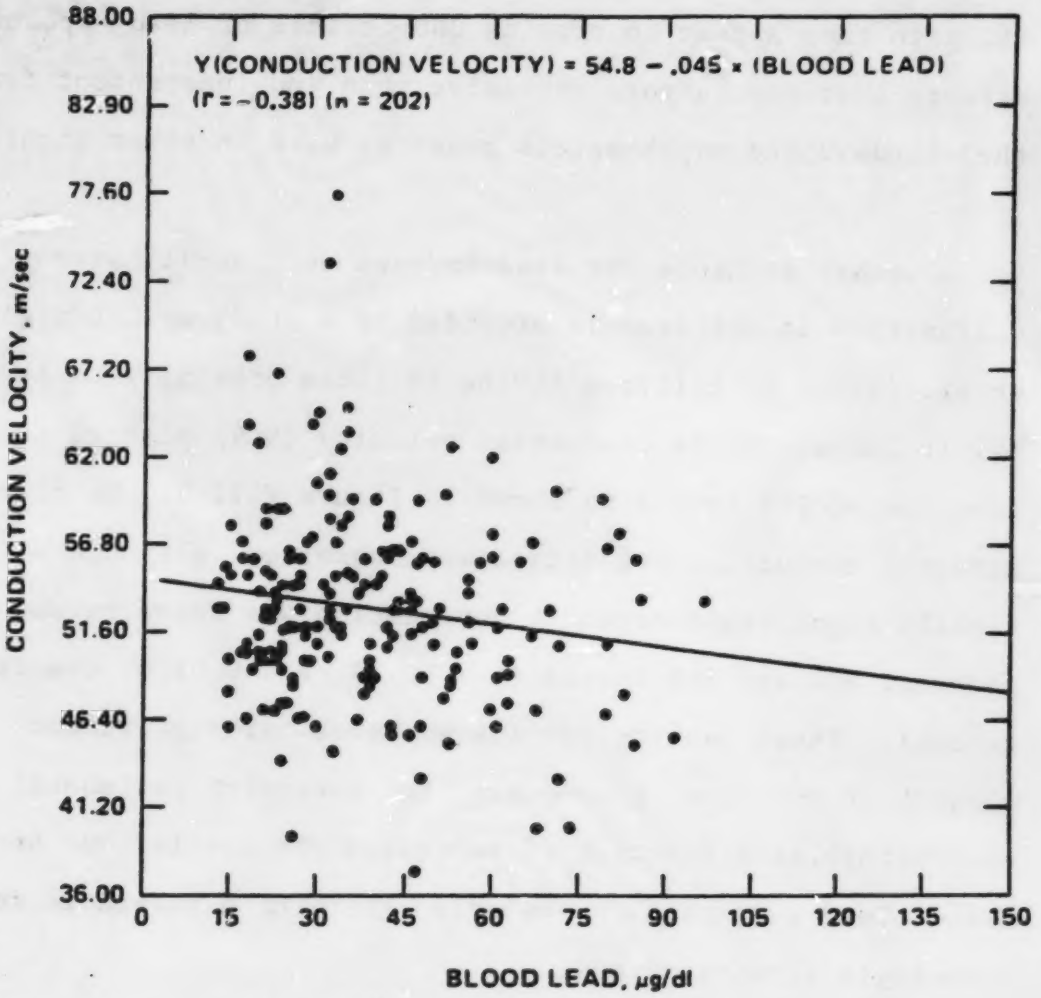
Source: Otto et al. (1981).

Figure VIII-2 Relation Between Blood Lead Level and Slow Wave Voltage

EEG measures was found in the initial (Benignus et al. 1981, Otto et al. 1981) or follow-up studies. Slow wave voltage and EEG gain thus appear to provide CNS indices of lead exposure effects that may be more sensitive than and independent from the standardized psychometric measures used in other studies.

Further evidence for lead-induced peripheral nerve dysfunction in children is provided by a study by Landrigan et al. (1976) of children living in close proximity to a smelter in Idaho. Nerve conduction velocity (NCV) plotted as a function of PbB levels is shown in Figure VIII-3. No clearly abnormal conduction velocities were observed, although a statistically significant negative correlation was found between peroneal NCV and PbB levels ($r = -0.38$, $P < 0.02$ by one-tailed t-test). These results provide evidence for significant slowing of NCV (and, presumably, for advancing peripheral neuropathy) as a function of increased PbB levels, but do not allow clear statements to be made regarding a threshold for pathologic slowing of NCV.

Prenatal exposure of the fetus at PbB levels below those causing fetotoxicity may result in damage to the brain. Beattie et al. (1975) identified 77 retarded children and 77 normal children matched for age, sex, and geography. Of 64 matched pairs, 11 of the retarded children came from homes in which the concentration of lead in the "first flush" water exceeded 800 ug/L. By contrast, none of the control children



Adapted from USEPA (1984).

Source: Landigan et al. (1976).

Figure VIII-3 Peroneal Nerve Conduction Velocity as a Function of Blood Lead Level

came from such homes. In a follow-up study, PbB values of the mental retardates, taken during the second week of life, were found to be significantly higher than those of control subjects (25.5 ± 8.9 vs. 20.9 ± 7.9 ug/dL) (Moore et al. 1977). When compared with the studies of children presumably suffering neurobehavioral deficits from direct exposure to lead, these studies suggest that the brain of the fetus is considerably more sensitive to the toxic effects of lead than the brain of the young child.

B. Quantification of Non-Carcinogenic Effects

1. One-Day Health Advisory

No studies were located which were suitable for calculation of a one-day Health Advisory for either children or adults. Values calculated below for ten-day Health Advisories will be taken as conservative estimates of appropriate one-day Health Advisories.

2. Ten-Day Health Advisory

Effects of short-term lead exposure are not well studied, but a number of workers have observed behavior or neurological changes in young animals exposed to lead through food or water at various times from post-natal day zero through post-natal day 150 (see Tables VIII-2 and VIII-3). The studies of Cory-

Slechta and Thompson (1979) and Cory-Slechta et al. (1981) have been selected to serve as the basis for calculation of the ten-day Health Advisory for children. These studies show that in weanling rats exposed to lead via drinking water, detectable behavioral effects are produced by water concentrations of lead as low as 0.0025% (25 mg/L) after as few as 30 days exposure. This corresponds to an average daily dose of about 2.5 mg/kg/day (assuming daily water consumption of 100 mL/kg) (Arrington 1972). Other studies (Tables VIII-2 and VIII-3) were not selected, since the estimated exposure levels were higher. No suitable study regarding short-term exposure in children was located. Gastrointestinal absorption rates do not need to be considered in this calculation, since the LOAEL is based on effects observed following oral ingestion.

The ten-day HA for the 10-kg child is calculated as follows:

Ten-Day Health Advisory for Child:

$$\frac{(2.5 \text{ mg/kg/day})(10 \text{ kg})}{(1 \text{ L/day})(1000)} = 0.025 \text{ mg/L (25 ug/L)}$$

where:

2.5 mg/kg/day = LOAEL, based on behavioral effects observed in weanling rats exposed to lead via drinking water (Cory-Slechta and Thompson 1979).

10 kg = assumed weight of a child.

1 L/day = assumed water consumption by a 10-kg child.

1000 = uncertainty factor. This factor was selected in accordance with ODW/NAS guidelines for use with a LOAEL from an animal study.

The studies by Govoni et al. (1979, 1980), Memo et al. (1980a, 1981) and Grant et al. (1980) have been selected to serve as the basis for calculation of the ten-day Health Advisory values for adults. These studies provide evidence for altered neurotransmitter metabolism and behavior traits in neonatal rats exposed to lead by supplying the dams with water containing 0.004% to 0.005% lead acetate during gestation and/or during post-natal development. This corresponds to an average daily dose to the mother of about 4 to 5 mg/kg/day (assuming consumption of 100 mL/kg/day) (Arrington 1972). On this basis, 4 mg/kg/day is taken as the LOAEL in animals. No suitable short-term study in humans was located. Gastrointestinal absorption rates do not need to be considered in calculation of the HA values, since the LOAEL is based on effects observed following oral exposure via drinking water.

The ten-day HA for the 70 kg adult is calculated as follows:

Ten-day Health Advisory for Adults:

$$\frac{(4\ \text{mg/kg/day})(70\ \text{kg})}{(2\ \text{L/day})(1000)} = 0.14\ \text{mg/L}\ (140\ \text{ug/L})$$

where:

4 mg/kg/day = LOAEL, based on altered neurotransmitter metabolism and behavior in rat pups born to dams exposed to lead via drinking water during gestation (Govoni et al. 1979, 1980, Memo et al. 1980a, 1981, Grant et al. 1980).

70 kg = assumed weight of an adult

2 L/day = assumed water consumption by a 70 kg adult

1000 = uncertainty factor. This uncertainty factor was selected in accordance with ODW/NAS guidelines for use with a LOAEL from an animal study.

3. Adjusted Acceptable Daily Intake

Because so many body systems are affected by chronic exposure to lead, and because so many studies provide data regarding the PbB threshold for toxic effects, it does not seem appropriate to select a single study as the basis for calculation of the ADI. Rather, it appears more appropriate to identify a "consensus" PbB value that represents the collective indication of the NOAEL based on all relevant studies in humans. Tables VIII-4 and VIII-5 summarize the adverse or potentially adverse effects associated with various PbB levels in adults and children, respectively. From these tables, it is apparent that effects on the enzymes of heme synthesis occur at very low PbB levels (10 ug/dL), and that subtle signs of neurological disorder begin to appear at 15 to 20 ug/dL in children and at 25 to 30 ug/dL in adults. A number of more obvious effects become manifest in several body systems at PbB levels of 40 ug/dL and higher. Taken as a whole, this body of data suggests that PbB

Table VIII-4 Summary of Health Effects[a] in Adults Following Chronic Lead Exposure

Lowest observed effect level (PbB)	Heme synthesis and hematological effects	Neurological effects	Renal system effects	Reproductive function effects	Gastrointestinal effects
100-120 µg/dL		Encephalopathic signs and symptoms	Chronic renal nephropathy		Overt gastrointestinal symptoms (colic, etc.)
80 µg/dL	Frank anemia				
60 µg/dL					
50 µg/dL	Reduced hemoglobin production	Overt subencephalopathic neurological symptoms		Altered testicular function	
40 µg/dL	Increased urinary ALA and elevated coproporphyrins				
30 µg/dL		Peripheral nerve dysfunction (slowed nerve conduction)			
25-30 µg/dL	Erythrocyte protoporphyrin (EP) elevation in males				
15-20 µg/dL	Erythrocyte protoporphyrin (EP) elevation in females				
<10 µg/dL	ALA-D inhibition				

[a]Abbreviations: PbB = blood lead concentrations.

Adapted from USEPA (1984).

Table VIII-5 Summary of Health Effects in Children Following Chronic Lead Exposure[a]

Lowest observed effect level (PbB)	Heme synthesis and hematological effects	Neurological effects	Renal system effects	Gastrointestinal effects
80-100 µg/dL		Encephalopathic signs and symptoms	Chronic nephropathy (amino-aciduria)	Colic, other overt gastrointestinal symptoms
70 µg/dL	Frank anemia			
60 µg/dL		Peripheral neuropathies		
50 µg/dL				
40 µg/dL	Reduced hemoglobin	Cognitive (CNS) deficits		
	Elevated coproporphyrin	Peripheral nerve dysfunction (slowed NCV's)		
	Increased urinary ALA			
30 µg/dL			Vitamin D metabolism interference	
15 µg/dL	Erythrocyte protoporphyrin elevation	Altered CNS electrophysiological responses		
10 µg/dL	ALA-D inhibition			
	Py-5-N activity inhibition			

[a]Abbreviations: PbB = blood lead concentrations; Py-5-N = pyrimidine-5'-nucleotidase.

Adapted from USEPA (1984).

values of 15 ug/dL should not be exceeded in children, and values of 25 ug/dL should not be exceeded in adults. In order to protect the fetus, however, it is necessary to set the PbB level in adults at 15 ug/dL as well, since several studies (Harris and Holley 1972, Gershanik et al. 1974, Hubermont et al. 1978) indicate that the ratio of fetal/ maternal PbB values is close to 1:1. Thus, a PbB level of 15 ug/dL is selected as the NOAEL.

Using a PbB value of 15 ug/dL as the NOAEL in humans, the average daily oral exposure that produces this PbB value can be calculated. A number of reports have been published which describe the relationship between average daily oral ingestion of lead and PbB values.

Studies in infants and toddlers are generally simpler than studies in older children or adults, due to the limited dietary intake (formula or breast milk) and the lower incidence of pica (which represents a significant source of lead ingestion in older children). Unfortunately, in three studies in infants and toddlers (Table VIII-6), significant differences were observed in the relationships (i.e., the slope of the line) between oral ingestion of lead from the diet (PbD) and blood lead levels (PbB). For example, it is not even clear whether the relationship is linear or curvilinear (dependent on the 1/3 power of daily intake). Most of the subjects in the Sherlock et al. (1982) and United Kingdom Central Directorate

Table VIII-6 Empirical Relationships between Dietary Lead Intake and Blood Lead Levels in Infants and Toddlers

Reference	Relationship[a]
Sherlock et al. (1982)	$PbB = 2.5 + 5\ (PbD)^{1/3}$
UKCD (1982)	$PbB = 17.1 + 0.56\ (PbD)$
	$PbB = 3.9 + 4.6\ (PbD)^{1/3}$
EPA (1984), based on Ryu et al. (1983)	$PbB = 0.16\ PbD$

[a]Abbreviations: PbB = blood lead concentration (µg/dL).
PbD = daily dietary intake (µg/day).

Adapted from USEPA (1984).

on Environmental Pollution (1982) studies received relatively high PbD levels (>300 ug/day). The fitted cube root equations give high slopes at lower PbD levels. On the other hand, the linear slope of the United Kingdom Central Directorate on Environmental Pollution (1982) study is probably an underestimate of the slope at low PbD levels. In the study by Ryu et al. (1983), a steady-state PbB value of about 7 ug/dL was observed in infants ingesting milk from cartons (total PbD = 16 ug/day). In another group of infants, a PbB value of about 14 ug/day was attained when the milk was supplied from cans (total PbD = 61 ug/day). From the increase in PbB (7 ug/dL) resulting from the increase in PbD (45 ug/day), the relationship shown in Table VIII-6 (PbB = 0.16 PbD) is derived. Since these PbD values are relatively low (16 to 61 ug/day) and involve PbB values in the range of interest (around 15 ug/dL), this equation is judged to be most appropriate for relating oral lead intake levels in infants and children to PbB values.

The relationship between oral ingestion of lead and PbB values in adults is even less certain. Tables VIII-7, VIII-8 and VIII-9 summarize some of the relevant studies. For dietary intake (Table VIII-5), most slopes relating PbD to PbB are about 0.02 ug/dL per ug/day. The relation between PbB values and water lead concentration (PbW) is not clearly defined and is often described as nonlinear (Tables VIII-8 and VIII-9). Many authors choose to fit cube root models to their data, although polynomial and logarithmic models are also used.

Table VIII-7 Studies Relating Blood Lead Levels to Experimental Dietary Intakes

Study	Subjects	Exposure	Chemical Form	Blood Level		Slope[a] (µg/dL per µg/day)
				Initial	Final	
Stuik (1974)	5 adult male students	20 µg Pb/kg/day - 21 days	Lead acetate	20.6	40.9	0.017[b,c]
	5 adult female students	20 µg Pb/kg/day - 21 days	Lead acetate	12.7	30.4	0.018[b,c]
	5 adult male students	Controls	Placebo	20.6	18.4	-
	5 adult female students	20 µg Pb/kg/day	Lead acetate	17.3	41.3	0.022
	5 adult male students	30 µg Pb/kg/day	Lead acetate	16.1	46.2	0.014
	5 adult female students	Controls	Placebo	∿17.0	∿17.0	-
Cools et al. (1976)	11 adult males	30 µg Pb/kg/day ∿7 days	Lead acetate	17.2	26.2	0.027[c]
	10 adult males	Controls	Placebo		∿19.0	-
Schlegel and Kufner (1979)	1 adult male	50 µg Pb/kg/day - 6 wk	Lead nitrate	16.5	64.0	0.014
	1 adult male	70 µg Pb/kg/day - 13 wk	Lead nitrate	12.4	30.4	0.004[d]
Gross (1979) analysis of Kehoe's experiments	1 adult male	300 µg/day	Lead acetate		-1	[0]
	1 adult male	1,000 µg/day	Lead acetate		+17	0.017
	1 adult male	2,000 µg/day	Lead acetate		+33	0.016
	1 adult male	3,000 µg/day	Lead acetate		+19	0.006[e]

[a] Exposure (µg/d) = Exposure (µg/kg/day) x 70 kg for males, 55 kg for females. Slope = (Final - Initial Blood Lead)/Exposure (µg/d).
[b] Corrected for decrease of 2.2 µg/dL in control males.
[c] Assumed mean life 40d. This increases slope estimate for short-term studies. Stuik Study I would be 0.042, 0.044 respectively for males, females.
[d] Assumed limited absorption of lead.
[e] Removed from exposure before equilibrium.

Adapted from USEPA (1984).

Table VIII-8 Studies Relating Blood Lead Levels (μg/dL) to First-Flush Water Lead (μg/L)

Study	Analysis	Model[a]	Estimated blood lead at PbW = 0	Predicted blood lead contribution (μg/dL) for a given water lead (μg/L) 5	10	25	50
Worth et al. (1981) study of 524 subjects in greater Boston. Water leads (standing water) ranged from <13 to 1,108 μg/L. Blood leads ranged from 6 to 71.	Worth et al. (1981)	ln (PbB) = 2.729 PbW - 4.699 $(PbW)^{2}$ + 2.116 $(PbW)^{3}$ + other terms for age, sex, education, dust (PbW is in mg/L).	20.5	0.3	0.6	1.4	2.7
	EPA	ln (PbB) = ln (.041 PbW - .000219 (PbW^{2}) + other terms for age, sex, education, dust)	21.1	0.2	0.4	1.0	2.1
Moore et al. (1979) study of 949 subjects from different areas of Scotland. Water leads were as high as 2,000 μg/L.	Moore et al. (1979)	PbB = 11.0 + 2.36 $(PbW)^{1/3}$	11.0	4.0	5.1	6.9	8.7
Hubermont et al. (1978) study of 70 pregnant women in rural Belgium. Water leads ranged from 0.2 to 1,228.5 μg/L. Blood leads ranged from 5.1 to 26.3 μg/dL.	Hubermont et al. (1978)	PbB = 9.62 +0.756 ln (PbW)	8.4[b]	2.4	3.0	3.7	4.2
U.K. Central Directorate (1982) study of 128 mothers in greater Glasgow. Water leads ranged from under <10, 1,060 μg/L. Blood leads ranged from 2 to 39 μg/dL.	U.K. Cen. Dir. (1982)	PbB = 13.2 + 1.8 $(PbW)^{1/3}$	13.2	3.1	3.9	5.3	6.6
	U.K. Cen. Dir. (1982)	PbB = 18.0 + 0.009 PbW	18.0	0.0	0.1	0.2	0.4
	EPA	ln (PbB) = ln (14.2 + 0.033 PbW - 0.000031 PbW^{2})	14.2	0.2	0.3	0.8	1.6
U.K. Central Directorate (1982) study of 126 infants (as above). Blood leads ranged from 1 to 51 μg/dL.	U.K. Cen. Dir. (1982)	PbB = 9.4 + 2.4 $(PbW)^{1/3}$	9.4	4.1	5.2	7.0	8.8
	U.K. Cen. Dir. (1982)	PbB = 17.2 + 0.018 PbW	17.1	0.1	0.2	0.4	0.9
	EPA	ln (PbB) = ln (12.0 + 0.050 PbW - 0.000045 PbW^{2})	12.0	0.2	0.5	1.2	2.4
Thomas et al. (1979) study of 115 adult Welsh females. Water leads ranged from <10 to 2,800 μg/dL. Blood leads ranged from 5 to 65 μg/dL.	EPA	ln (PbB) = (14.9 + 0.041 PbW - 0.000012 PbW^{2})	14.9	0.2	0.4	1.0	2.0
Moore (1977) study of 75 residents of a Glasgow tenement.	Moore (1977)	PbB = 15.7 + 0.015 PbW	15.7	0.1	0.2	0.4	0.8
Pocock et al. (1983) study of 7,735 men aged 40-59 in Great Britain. Water leads restricted to <100 μg/L.	Pocock et al. (1983)	PbB = 14.48 + 0.062 PbW	14.5	0.3	0.6	1.6	3.1

[a] Abbreviations: PbB = blood lead concentration (μg/dL), PbW = water lead concentration (μg/L).
[b] Minimum water lead of 0.2 μg/dL used instead of 0.

Adapted from USEPA (1984).

Table VIII-9 Studies Relating Blood Lead Levels (µg/dL) to Running Water Lead (µg/dL)

Study	Analysis	Model[a]	Estimated blood lead at PbW = 0	Predicted blood lead contribution (µg/dL for a given water lead (µg/L) 5	10	25	50
Worth et al. (1981) study of 524 subjects in greater Boston. Water leads (standing water) ranged from <13 to 1,108 µg/L. Blood leads ranged from 6 to 71.	EPA	ln (PbB) = (0.0425 PbW + other terms for age, sex, education and dust)	21.3	0.2	0.4	1.1	2.1
Worth et al. (1981) study restricted to 390 subjects aged 20 or older.	U.S. EPA (1980)	$PbB = 14.33 + 2.541\ (PbW)^{1/3}$	14.3	4.4	5.4	7.4	9.4
	EPA	ln (PbB) = ln (18.6 + 0.071 PbW)	18.6	0.4	0.7	1.8	3.6
	EPA	ln (PbB) = ln (0.073 PbW + other terms for sex, education and dust)	18.8	0.4	0.7	1.8	3.7
Worth et al. (1981) study restricted to 249 females ages 20 to 50.	U.S. EPA (1980)	$PbB = 13.38 + 2.487\ (PbW)^{1/3}$	13.4	4.3	5.4	7.3	9.2
	EPA	ln (PbB) = ln (17.6 + 0.067 PbW)	17.6	0.3	0.7	1.7	3.4
	EPA	ln (PbB) = (0.067 PbW + other terms for education and dust)	17.6	0.3	0.7	1.7	3.4
U.K. Central Directorate (1982) study of 128 mothers in greater Glasgow. Water leads ranged from under 20 to 720 µg/L. Blood leads ranged from 1 to 39 µg/dL.	U.K. Cen. Dir. (1982)	$PbB = 12.8 + 1.8\ (PbW)^{1/3}$	12.8	3.1	3.9	5.3	6.6
	U.K. Cen. Dir. (1982)	PbB = 18.1 + .014 PbW	18.1	0.1	0.4	0.4	0.7
	EPA	ln (PbB) = ln (13.4 + 0.071 PbW $-0.000104\ PbW^2$)	13.4	0.4	0.7	0.7	3.3
Moore (1977) study of 75 residents of a Glasgow tenement.	Moore (1977)	PbB = 16.6 + 0.02 PbW	16.6	0.1	0.2	0.5	1.0
Sherlock et al. (1982) study of 114 adult women. Blood leads ranged <5 to >61 µg/dL. Kettle water leads ranged from <10 to >2,570 µg/L.	Sherlock et al. (1982)	$PbB = 4.7 + 2.78\ (PbW)^{1/3}$	4.7	4.8	6.0	8.1	10.2
	EPA	ln (PbB) = ln (11.5 + 0.033 PbW $-0.00001\ PbW^2$)	11.5	0.2	0.3	0.8	1.6
Sherlock et al. (1984) follow-up study.	Sherlock et al. (1984)	$PbB = 5.6 + 2.62\ (PbW)^{1/3}$	5.6	4.5	5.6	7.7	9.7

[a]Minimum water lead of 0.2 µg/dL used instead of 0.

Adapted from USEPA (1984).

Unfortunately, the form of the model employed greatly influences the estimated contributions to PbB from relatively low PbW values. The only study that determines the relationship based on low drinking water lead values (<100 ug/L) is that by Pocock et al. (1983). The data from this study suggest that in this lower concentration range, the relationship is linear. Furthermore, the estimated contributions to PbB levels from this study are roughly consistent with the polynomial models from other studies. For these reasons, the Pocock et al. (1983) slope of 0.06 is considered to be the most appropriate for use at low water lead concentrations.

Calculation of ADI for Infants and Children:

Using the relationship derived from the data of Ryu et al. (1983) (PbB = 0.16 PbD), the ADI for infants and children may be calculated as follows:

$$\frac{(15 \text{ ug/dL})}{[(1 \text{ ug/dL})/(0.16 \text{ ug/day})](5)} = 19 \text{ ug/day}$$

where:

15 ug/dL = blood lead level (PbB) at which no adverse effects are observed (see Tables VIII-4 and VIII-5).

$\frac{1 \text{ ug/dL}}{0.16 \text{ ug/day}}$ = relation between lead intake in the diet (PbD) and blood lead level (PbB) in infants (Ryu et al. 1983).

5 = uncertainty factor. This factor was selected for account for intra-human variability, uncertainty with respect to selection of the NOAEL (as PbB) and uncertainty with respect to calculation of an oral intake equivalent to the NOAEL. The rationale for this uncertainty factor is detailed below.

According to ODW/NAS guidelines (see Page VIII-3), an uncertainty factor of 10 is normally employed when a NOAEL in humans is used as the basis for calculation of the ADI and AADI values. This factor is intended to account for intra-human variation in sensitivity to the toxicant. However, in this case, the NOAEL has been selected in order to protect the most sensitive portion of the population (infants and pregnant women). Therefore, it is judged that no uncertainty factor is required to account for this consideration. There are, however, two other sources of uncertainty associated with this calculation that do require consideration. The first source of uncertainty is selection of the blood lead level (PbB) which represents a NOAEL in children and pregnant females. The adverse effects of lead appear to be described by a dose-response continuum with no clear threshold value. Because the PbB value selected (15 ug/dL) is associated only with subtle, pre-clinical effects, it is judged that there is relatively little uncertainty associated with selection of this value. The second source of uncertainty lies in the calculation of an oral intake which corresponds to the selected PbB value. Since there is considerable variation in the mathematical relationships which have been derived between oral lead intake and PbB, it is judged that significant uncertainty exists in this calculation. An overall uncertainty factor of 5 was selected to account for all of these considerations.

Calculation of ADI for Adults:

Using the relationship derived from the data of Pocock et al. (1983) (PbB = 0.062 PbW), the ADI for adults may be calculated as follows:

$$\frac{(15 \text{ ug/dL})}{[(1 \text{ ug/dL})/(0.062 \text{ ug/day})](5)} = 48 \text{ ug/day}$$

where:

15 ug/dL = blood lead level at which no adverse effects are observed (see Tables VIII-4 and VIII-5).

$\frac{1 \text{ ug/dL}}{0.062 \text{ ug/day}}$ = relation between lead intake in water (PbW) and blood lead level (PbB) in adults (Pocock et al. 1983).

5 = uncertainty factor. The basis of this factor is detailed above, in the calculation of the ADI for children.

Calculation of AADI:

Using 19 ug/day as the ADI in infants and children, and assuming consumption of one liter of water per day by a 10-kg child, the AADI for infants and children is calculated as follows:

$$\frac{19 \text{ ug/day}}{1 \text{ L/day}} = 19 \text{ ug/L}$$

Using 48 ug/day as the ADI in adults, and assuming consumption of two liters of water per day by a 70-kg adult, the AADI for adults is calculated as follows:

$$\frac{48 \text{ ug/day}}{2 \text{ L/day}} = 24 \text{ ug/L}$$

Choosing the lower value in order to protect both groups, the AADI for both children and adults is taken to be 19 ug/L.

Consideration of Relative Source Data:

The calculations above assume that 100% of the lead exposure occurs from ingestion of drinking water. This is nearly correct for infants consuming formula prepared with water. However, studies of the routes of lead exposure in older children and adults have found that inhalation of air-borne lead, ingestion of lead in food and ingestion of lead in dust and other non-food substances (paint chips, etc.) are significant sources of exposure. Table VIII-10 summarizes the average baseline exposure from these sources. This baseline exposure is considered unavoidable without a generalized reduction of lead content in air and canned foods. From Table VIII-10, it can be seen that the amount of lead ingested in water under baseline conditions is about 15% of the total intake in children and about 31% of the total in adults. Table VIII-11 lists the sources and amounts of additional lead exposure which may occur in some cases. Most of these additional exposures derive from air or dust; few are from food or water. Several studies have found that, except in unusual cases, an average American consumes about 100 ug of lead per day, of which about 80 to 90 ug is from food, air and dust. This intake exceeds both the ADI in children (19 ug/day) and the ADI in adults (48 ug/day). In this situation, the ADI from water may be taken to be 15%

Table VIII-10 Baseline Lead Exposure in Humans

Source	2-year-old child		Adult male	
	µg/day	% Total	µg/day	% Total
Air	0.5	1	1.0	2
Food	18.9	40	35.8	59
Dust	21.0	44	4.5	7
Water	6.9	15	18.9	31
Total	47.3	100	60.2	100

Adapted from USEPA (1984).

Table VIII-11 Summary of Additional Human Exposures to Lead

Source	Total lead consumed (µg/day)	
	Child	Adult
Baseline exposure (Air, food, water, dust)	47	60
Additional exposure due to:		
Urban atmosphere	91	28
Family gardens	48	120
Lead paints	110	17
Residence near smelter	2,200	250
Smoking	-	30
Wine consumption	-	100
Occupational	-	1,100
Total	47-2,496	60-1,705

Adapted from USEPA (1984).

of the total ADI, which is the value for baseline exposure through water in children (see Table VIII-10). The AADI value is then calculated as follows:

AADI:

$$\frac{(0.15)(19\ ug/day)}{(1\ L/day)} = 3\ ug/L$$

where:

19 ug/day = ADI which protects both children and adults.

1 L/day = assumed water consumption by a 10-kg child.

0.15 = assumed fraction of total ADI which may be contributed by water.

C. Carcinogenic Effects

Fifteen studies of cytogenetic abnormalities in persons exposed to lead have been summarized (IARC 1980). Positive results were reported in nine of these studies, whereas six reported negative results. For example, O'Riordan and Evans (1974) reported no significant chromosomal damage in male workers with PbB values from 40 to 120 ug/dL. However, Forni et al. (1976) found the incidence of abnormal metaphases doubled ($P < 0.05$) in workers exposed to air lead levels of more than 0.8 mg/m^3 for one month; the incidence increased further for two months and remained elevated for up to seven months. Blood lead levels increased from an initial mean of 34 ug/dL to 45 ug/dL in the first month, although this change was not statistically significant. Erythrocyte ALAD activity was reduced almost 50% during the first month of exposure

($P < 0.05$), and decreased further in subsequent months. The reason for these conflicting findings is not clear. Deknudt et al. (1977) suggested that ancillary factors (e.g., the level of calcium intake) may be critical.

A number of studies of the carcinogenic potential of various lead salts in animals are summarized in Table VIII-12. The most common observation was increased frequency of renal tumors, although evidence of tumors in other tissues has been noted. The doses of salt producing these effects were quite high, generally 0.1% to 1% in the diet (equivalent to about 50 to 500 mg Pb/kg/day, assuming consumption of 50 g food/kg body weight).

The study most useful in establishing a quantitative relationship between lead ingestion and frequency of renal tumors is the report by Azar et al. (1973). The data from this report are summarized in Table VIII-13. A dose-dependent increase in renal tumor frequency in male rats was observed over the range of 500 to 2,000 ppm Pb (as lead acetate) in the diet. It should be noted that these doses are associated with moderate to severe non-carcinogenic effects in rats.

Several epidemiological studies of industrial workers, for whom the potential for lead exposure is typically greater than for a "normal population," have been conducted to evaluate the role of lead in the induction of human neoplasia (Cooper

Table VIII-12 Summary of Studies on the Incidence of Tumors in Experimental Animals Exposed to Lead Compounds

Species	Pb Compound	Dose and mode[a]	Incidence (and type) of neoplasms	Reference
Rat	Pb phosphate	120-680 mg (total dose s.c.)	19/29 (renal tumors)	Zollinger (1953)
Rat	Pb acetate	1% (in diet)	15/16 (kidney tumors) 14/16 (renal carcinomas)	Boyland et al. (1962)
Rat	Pb subacetate	0.1% and 1.0% (in diet)	11/32 (renal tumors) 13/24 (renal tumors)	Van Esch et al. (1962)
Rat	Pb phosphate	1.3 g (total dosage s.c.)	29/80 (renal tumors)	Balo et al. (1965)
Rat	Pb subacetate	0.5 - 1% (in diet)	14/24 (renal tumors)	Hass et al. (1967)
Rat	Pb subacetate	1% (in diet)	31/40 (renal tumors)	Mao and Molnar (1967)
Rat	Pb acetate	3 mg/day for 2 months; 4 mg/day for 16 months (p.o.)	72/126 (renal tumors) 23/94 males (testicular [Leydig cell] tumors)	Zawirska and Medraś (1968)
Hamster	Pb subacetate	1.0% (in 0.5% diet)	No significant incidence of renal neoplasms	Van Esch and Kroes (1969)
Mouse	Pb subacetate	0.1% and 1.0% (in diet)	7/25 (renal carcinomas) at 0.1%; substantial death at 1.0%	Van Esch and Kroes (1969)
Rat	Pb nitrate	25 g/L in drinking water	No significant incidence of tumors	Schroeder et al. (1970)
Rat	Pb acetate	3 mg/day (p.o.)	89/94 (renal, pituitary, cerebral gliomas, adrenal, thyroid, prostatic, mammary tumors)	Zawirska and Medraś, 1972
Rat	Pb acetate	0, 10, 50, 100, 1,000, 2,000 ppm (in diet) for 2 yr	No tumors 0-100 ppm; 5/50 (renal tumors) at 500 ppm; 10/20 at 1,000 ppm; 16/20 males, 7/20 females at 2,000 ppm	Azar et al. (1973)

[a]Abbreviations: S.C. = subcutaneous injection; p.o. = per os (gavage).

Table VIII-12 - continued

Species	Pb Compound	Dose and mode	Incidence (and type) of neoplasms	Reference
Rat	Pb chromate	10 mg (p.o.) 2 times each month	5/47 (1 lymphoma, 4 leukemias)	Furst et al. (1976)
		10 mg/monthly for 9 months; then 3 monthly injections of 5 mg	1/50 (fibrosarcoma)	

Adapted from USEPA (1984).

Table VIII-13 Mortality and Kidney Tumors in Rats Fed Lead Acetate for Two Years

Pb in diet (ppm)	Average daily dose (mg/kg/day)[a]	No. of rats of each sex	% Mortality		% Kidney tumors	
			Male	Female	Male	Female
5	0.3	100	37	34	0	0
18	0.9	50	36	30	0	0
62	3.1	50	36	28	0	0
141	7.1	50	36	28	0	0
548	27.4	50	52	36	10	0
3	0.2	20	50	35	0	0
1,130	56.5	20	50	50	50	0
2,102	105.1	20	80	35	80	35

[a]Assuming consumption of 50 g food/kg body weight.
[b]Includes rats that either died or were sacrificed *in extremis*.

Adpated from Azar et al. (1973).

1976, Cooper 1981, Cooper and Gaffey 1975, Chrusciel 1975, Dingwall-Fordyce and Lane 1963, Lane 1964, McMichael and Johnson 1982, Neal et al. 1941, Nelson et al. 1982). In general, these studies made no attempt to consider the types of lead compounds to which workers were exposed, or to determine probable routes of exposure. While a number of these studies found an association between lead exposure and the frequency of various cancer types, no study was sufficiently free of confounding factors to permit a clear conclusion.

The International Agency for Research on Cancer (IARC) has performed as assessment of the degree of evidence for the carcinogenicity of lead and lead compounds in humans and experimental animals (WHO 1982). This assessment concluded that lead and lead compounds are Group 3 compounds (sufficient evidence for carcinogenicity of some lead salts in animals, but inadequate evidence for carcinogenicity in humans).

D. Quantification of Carcinogenic Risk

Although some lead salts are clearly associated with increased renal tumor frequency in animals, no quantitative estimate of excess cancer risk was located. The data in Table VIII-12 indicate that relatively high lead intake levels are required to produce increased tumor rates, and it seems probable that the non-carcinogenic effects of lead occur at lower levels.

E. Existing Guidelines and Standards

The current MCL for lead in drinking water is 50 ug/L (USEPA 1976). This is based on the recognition that although water is not normally a major route of lead exposure, it nevertheless "would seem wise at this time to continue to limit the lead in water to as low a level as practical" (USEPA 1976). The WHO European standard for lead is 100 ug/L, as is the USSR standard.

The National Academy of Sciences (NAS 1977) concluded that the "no-observed-adverse-health-effect level cannot be set with assurance at any value greater than 0.025 mg/L" (25 ug/L), noting that:

> ". . . the present limit of 50 ug/L may not, in view of other sources of environmental exposure, provide a sufficient margin of safety, particularly for fetuses and young growing children. Although further studies will be necessary to arrive at a reasonable limit, it is suggested that the limit be lowered."

F. Special Considerations

1. High Risk Subpopulations

Numerous studies based on neurobehavioral, morphological or biochemical endpoints all suggest that the order of human susceptibility to the neurotoxic effects of lead is: young > adult; female > male. Animal studies also have pointed to the

perinatal period of ontogeny as a time of particular sensitivity to lead. The precise boundaries of a critical period for lead exposure are not yet clear, and may vary depending on the species and function or endpoint that is being assessed. Nevertheless, there is general agreement that human infants and toddlers below the age of three years are at special risk because of increased opportunity for exposure through pica and increased rates of lead absorption.

In addition, women of child-bearing age are considered a high risk subpopulation, since the ratio of fetal/maternal PbB values is near 1:1. For these reasons, the AADI is set to protect all groups, including the fetus in utero, infants and children.

2. Interactions

A number of compounds are known to influence the toxicity of orally-ingested lead. In most cases, this is because the absorption of lead from the diet is affected by the compounds. For example, studies in animals and humans have shown that low dietary levels of calcium, phosphate, copper or zinc all tend to cause increased gastrointestinal absorption and retention of lead. Increased levels of vitamin D also cause increased lead absorption. Increased ingestion of dietary lipids (especially polyunsaturates) causes increased absorption, as do certain milk components (particularly lactose). The relation-

ship between dietary protein levels and lead absorption is not clear, since both decreased and increased protein intake cause increased lead absorption. The dietary deficiencies which cause increased lead absorption are most prevalent in children, and especially in poor children.

3. Beneficial Effects

No beneficial effects of lead in mammals are recognized.

4. Other Factors

A large fraction of the lead in the environment which poses an exposure risk to humans is anthropogenic in origin. Of particular concern is lead in air, which is inhaled directly, or which settles and is subsequently ingested as dust. Another major concern is lead which enters food from soldered containers. While lead ingestion through water may be important in some cases, it normally does not represent the principal route of human exposure.

G. Summary

The recommended HA and AADI values for lead are summarized in Table VIII-14.

Table VIII-14 Summary of Quantification of Toxicological Effects

	Drinking water concentration (µg/L)	
	10-kg child	70-kg adult
One-Day Health Advisory	25[a]	140[b]
Ten-Day Health Advisory	25[a]	140[b]
AADI (100% from water)	19	—[c]
AADI (15% from water)	3	—[c]

[a]Based on studies by Cory-Slechta and Thompson (1979).
[b]Based on studies by Govoni et al (1979, 1980), Memo et al. (1980a, 1981) and Grant et al. (1980).
[c]Calculated value is higher than for the child, so the lower value (for the child) is adopted in order to protect both groups.

IX. REFERENCES

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